

CLAIMS

1. A transgenic ungulate comprising one or more nucleic acids encoding all or part of a xenogenous immunoglobulin (Ig) gene which undergoes rearrangement and expresses more than one xenogenous Ig molecule.
- 5 2. The ungulate of claim 1, wherein said xenogenous Ig molecule is a human Ig molecule.
3. The ungulate of claim 1, wherein said nucleic acid is contained within a chromosome fragment.
4. The ungulate of claim 3, wherein said chromosome fragment is a Δ HAC or
10 $\Delta\Delta$ HAC.
5. The ungulate of claim 1, wherein said ungulate is a bovine, ovine, porcine, or caprine.
6. A transgenic ungulate comprising a mutation that reduces the expression of an endogenous antibody.
- 15 7. The ungulate of claim 6, wherein said mutation reduces the expression of functional IgM heavy chain or reduces the expression of functional Ig light chain.
8. The ungulate of claim 6, comprising one or more nucleic acid encoding all or part of a xenogenous Ig gene which undergoes rearrangement and expresses more than one xenogenous Ig molecule.
- 20 9. The ungulate of claim 6, wherein said ungulate is a bovine, ovine, porcine, or caprine.
10. An ungulate somatic cell comprising one or more nucleic acids encoding all or part of a xenogenous Ig gene, wherein said gene is capable of undergoing rearrangement and expressing one or more xenogenous Ig molecules in B cells.
- 25 11. The cell of claim 10, wherein said nucleic acid encodes a xenogenous antibody.

12. The cell of claim 10, wherein said nucleic acid is contained in a chromosome fragment.

13. The cell of claim 10, wherein said cell is a fetal fibroblast or B-cell.

14. The cell of claim 10, wherein said ungulate is a bovine, ovine, porcine, or
5 caprine.

15. An ungulate somatic cell comprising a mutation in a nucleic acid encoding an Ig heavy and/or light chain.

16. The cell of claim 15, comprising a mutation in both alleles of said IgM heavy chain or said light chain.

10 17. The cell of claim 15, further comprising one or more nucleic acids encoding all or part of xenogenous Ig gene, wherein said gene is capable of undergoing rearrangement and expressing one or more xenogenous Ig molecules in B cells.

18. The cell of claim 15, wherein said cell is a fetal fibroblast or a B-cell.

19. The cell of claim 15, wherein said ungulate is a bovine, ovine, porcine, or
15 caprine.

20. A hybridoma formed from the fusion of the B-cell of claim 13 or 18 with a myeloma cell.

21. A method of producing antibodies, said method comprising the steps of:

(a) administering one or more antigens of interest to an ungulate comprising
20 nucleic acid encoding a xenogenous antibody gene locus, wherein the nucleic acid segments in said gene locus undergo rearrangement resulting in the production of antibodies specific for said antigen; and

(b) recovering said antibodies from said ungulate.

25 22. The method of claim 21, wherein said ungulate comprises a mutation that reduces the expression of an endogenous antibody.

23. The method of claim 21, wherein said nucleic acid is contained in a chromosome fragment.

24. The method of claim 21, wherein said nucleic acid is a human nucleic acid.

25. The method of claim 21, wherein said ungulate is a bovine, ovine, porcine, or caprine.

26. A method of producing antibodies, said method comprising recovering
5 xenogenous antibodies from an ungulate comprising nucleic acid encoding a xenogenous antibody gene locus, wherein the nucleic acid segments in said gene locus undergo rearrangement resulting in the production of xenogenous antibodies.

27. The method of claim 26, wherein said ungulate comprises a mutation that reduces the expression of an endogenous antibody.

10 28. The method of claim 26, wherein said nucleic acid is contained in a chromosome fragment.

29. The method of claim 26, wherein said ungulate is a bovine, ovine, porcine, or caprine.

30. A method of producing a transgenic ungulate, said method comprising the
15 steps of:

(a) inserting a cell, a chromatin mass from a cell, or a nucleus from a cell into an oocyte, wherein said cell comprises a first mutation in an endogenous antibody heavy chain and/or light chain nucleic acid; and

(b) transferring said oocyte or an embryo formed from said oocyte into the uterus
20 of a host ungulate under conditions that allow said oocyte or said embryo to develop into a fetus.

31. The method of claim 30, further comprising the steps of:

(c) isolating a cell from said embryo, said fetus, or an offspring produced from said fetus;

25 (d) introducing a second mutation in an endogenous antibody heavy chain and/or light chain nucleic acid in said cell;

(e) inserting said cell, a chromatin mass from said cell, or a nucleus from said cell into an oocyte; and

(f) transferring said oocyte or an embryo formed from said oocyte into the uterus of a host ungulate under conditions that allow said oocyte or said embryo to develop into a fetus.

32. The method of claim 30, wherein said cell comprises one or more nucleic acids encoding all or part of a xenogenous Ig gene, wherein said gene is capable of undergoing rearrangement and expressing one or more xenogenous Ig molecules in B cells, and wherein said cell is inserted into said oocyte.

33. The method of claim 30, wherein said ungulate is a bovine, ovine, porcine, or caprine.

34. A method of producing a transgenic ungulate, said method comprising the steps of:

(a) inserting a cell having one or more xenogenous nucleic acids into an oocyte; wherein said xenogenous nucleic acid encodes all or part of a xenogenous Ig gene; said gene capable of undergoing rearrangement and expressing more than one xenogenous Ig molecule in B cells; and

(b) transferring said oocyte or an embryo formed from said oocyte into the uterus of a host ungulate under conditions that allow said oocyte or said embryo to develop into a fetus.

35. The method of claim 34, wherein said immunoglobulin chain is expressed in serum and/or milk.

36. The method of claim 34, wherein said nucleic acid is contained in a chromosome fragment.

37. The method of claim 34, wherein said xenogenous antibody is a human antibody.

38. The method of claim 34, wherein said ungulate is a bovine, ovine, porcine, or caprine.

39. A method of producing a transgenic ungulate, said method comprising the steps of:

(a) inserting a cell, a chromatin mass from a cell, or a nucleus from a cell into an oocyte, wherein said cell comprises a first mutation in an endogenous gene, wherein said gene is not naturally expressed by said cell; and

(b) transferring said oocyte or an embryo formed from said oocyte into the uterus
5 of a host ungulate under conditions that allow said oocyte or said embryo to develop into a fetus.

40. The method of claim 39, further comprising the steps of:

(c) isolating a cell from said embryo, said fetus, or an offspring produced from said fetus;

10 (d) introducing a second mutation in an endogenous gene in said cell;

(e) inserting said cell, a chromatin mass from said cell, or a nucleus from said cell into an oocyte;; and

(f) transferring said oocyte or an embryo formed from said oocyte into the uterus
15 of a host ungulate under conditions that allow said oocyte or said embryo to develop into a fetus.

41. The method of claim 39, wherein said cell is a fibroblast.

42. The method of claim 39, wherein said gene encodes an antibody.

43. The method of claim 39, wherein said gene encodes alpha-(1,3)-galactosyltransferase.

20 44. The method of claim 39, wherein said gene encodes prion protein.

45. The method of claim 39, wherein said gene encodes J chain.

46. The method of claim 39, wherein said cell comprises a nucleic acid encoding an exogenous J chain.

47. Ungulate antiserum comprising polyclonal human immunoglobulins (Igs).

25 48. Ungulate milk comprising polyclonal human Igs.